UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: August 24, 2005

MEMORANDUM

Subject: EPA File Symbol: 2724-LNU RF2004 (CCSO)
DP Barcode: D316839
Decision No.: 355865
PC Codes: 128965, Etofenprox (40%); 105402, S-Methoprene (3.6%)

From: Byron T. Backus, Ph.D. Byron T. Backus 8-24-2005
Technical Review Branch
Registration Division (7505C)
JCW 8/26/05

To: Bonaventure Akinlosotu/George LaRocca RM 13
Insecticide Branch
Registration Division (7505C)

Registrant: Wellmark International

FORMULATION DECLARATION FROM LABEL:

Active Ingredient(s):	% by wt
Etofenprox (CAS 80844-07-1)	40.0%
(S)-Methoprene (CAS 65733-16-6)	3.6%
Inert Ingredients:	56.4%
Total:	100.00%

ACTION REQUESTED:

The Risk Manager requests:

"...Please review the accompanying data pkg (MRID 46513409 - a companion animal safety evaluation in cats) and enclosed supporting documents for RF2004 (CCSO), EPA File Symbol 2724-LNU."

BACKGROUND:

This companion animal safety study (MRID 46513409) in this package was conducted on 12-week old kittens. Each of these kittens weighed less than 5 lbs. The proposed label directions state that a 1 mL dose is to be used on cats and kittens under 5 lbs and a 2 mL dose is to be used on cats and kittens of 5 lbs and over.

As noted in the registrant's cover letter dated March 31, 2005, the Agency registered a similar cat topical product containing Etofenprox with another IGR in May 2004 (EPA Reg. No. 69332-3).

COMMENTS AND RECOMMENDATIONS:

1. In the companion animal safety study in MRID 46513409, there was no indication of any dose-related effect involving food consumption, body weights, body weight gains, hematology and/or clinical chemistry parameters. Observations of excessive salivation were noted in one male and one female of the control group a few minutes after dosing, and for one male in this group about 20 minutes after dosing. One control female had salivation at the 1-hour observation and one 5X female showed this at the 2-hour observation. These episodes of salivation lasted no more than 10 minutes, and are ascribed (see p. 17 of MRID 46513409) to oral contact (ingestion) with the control or test material.

2. A small (5 mm or less) sore or scabbing was noted at the application site on Day 7 or later for one Group 4 (5X) male and one Group 4 (5X) female, and in one Group 3 (3X) female. In each case the lesion scabbed over and by Day 14 was barely detectable. It is stated (p. 17 of MRID 46513409) that the cause of these sores is unknown. These sores and scabbing are consistent with scratching at the application site. Etofenprox is structurally similar to pyrethroids which are known to cause sensations (such as tingling, burning, itching or numbness) at dermal exposure sites. Fully-grown cats would be capable of more vigorous scratching than 12-week old kittens, and (if ≥5 lbs) would be receiving a 2 mL dose.

3. TRB concludes that this companion animal safety study (OPPTS) is acceptable in demonstrating an adequate margin of safety (at least 5X) between the exposure associated with the proposed application rate for this formulation (1.0 mL) in kittens between the age of 12 weeks and 6 months weighing less than 5 lbs and that at which significant systemic effects may occur. However, it does not support the proposed use application rate (2.0 mL) in adult cats weighing ≥ 5 lbs, as none of the animals tested were adults or in this weight category. The 870.7200 Guidelines specify that: "Studies should be performed on healthy dogs and cats representative of the classes of dogs and cats (size, weight range, sex, or age) for which the product is intended." In addition, there are concerns regarding the possibility of sores and scabbing following a single 2.0 mL application. An appropriate study (including 1X, 3X and 5X multiples of 2.0 mL dosages) should be submitted for adult cats >5 lbs as supporting data to fully support the proposed application rates of this product.

EPA Primary Reviewer: Byron T. Backus, Ph.D. Signature: Byron T. Backus
Technical Review Branch, Registration Division (7505C) Date 8-24-2005
EPA Secondary Reviewer: John Redden, M.S. Signature: John Redden
Technical Review Branch, Registration Division (7505C) Date 8/26/05

DATA EVALUATION RECORD

STUDY TYPE: Companion Animal Safety - Cats OPPTS 870.7200
PC CODES: 128965 (Etofenprox), 105402 (S-Methoprene)
DP BARCODE: D316839 **RISK MANAGER:** (EPA): 13 **DECISION NO.:**355865

PRODUCT AND TEST MATERIAL: RF2004 [CCSO]; From information on p. 92 of MRID 46513409 the test material contained 40.30% Etofenprox and 3.55% (S)-Methoprene, consistent with the label declaration (3.6% S-Methoprene; 40.0% Etofenprox) for the proposed product RF2004 (CCSO). The test material is further described (p. 12 of MRID 46513409) as a liquid.

CITATION: Bassett, J. (2004) A Companion Animal Safety Evaluation Study in Cats with RF2004 [CCSO]. Project No. 016064, 2971, 016064/1. 817-008. Unpublished study prepared by Ricerca Biosciences, LLC, Concord OH 44077-1000. Study Completion Date: 8 December 2004; MRID 46513409.

SPONSOR: Wellmark International, 1100 East Woodfield Rd, Schaumburg, IL

EXECUTIVE SUMMARY: In a companion animal safety study (MRID 46513409), 4 groups, each containing 12 (6/sex) approximately 12-week old "young adult animals" (source: Liberty Research, Waverly, NY; males: 1295-1765 g; females: 1068-1876 g) were treated at 0X (Group 1: 5.0 mL of the formulation without active ingredients); 1X (Group 2: 1.0 mL); 3X (Group 3: 3.0 mL); and 5X (Group 4: 5.0 mL) of the proposed product with actives. The test material was applied to an area on the mid-dorsal back (between shoulders) on Day 0, with subsequent 14-day observation.

According to proposed label directions the product would be applied to the fur of the cat or kitten on the back of the neck at the base of the skull. Labeling specifies the use of a 1 mL dose for cats and kittens weighing less than 5 lbs, and a 2 mL dose for cats or kittens weighing more than 5 lbs.

On the day of dosing (Day 0); four clinical observations were made at 1, 2, 3 and 4 hours after postdose. Otherwise, clinical observations were conducted twice daily, once in the AM and once in the PM [approximately x hours apart].

Individual body weights were measured on Days -12, -5, -1, 0, 7 and 14. Individual food consumption was measured on a daily basis for Days -7, -6, -4 and then daily thereafter through Day 14. Blood samples were taken once pretest (Day -5) and then on Day 1 (approximately 24 hours postdose).

There was no mortality and there was no indication of systemic toxicity. Clinical observations seen in all groups included sporadic diarrhea and soft feces. Observations of excessive

salivation were noted in one male and one female of the control group a few minutes after dosing, and for one male in this group about 20 minutes after dosing. One control female had salivation at the 1-hour observation and one 5X female showed this at the 2-hour observation. These episodes of salivation lasted no more than 10 minutes, and are ascribed (see p. 17 of MRID 46513409) to oral contact (ingestion) with the control or test material.

Overall, all kittens gained weight throughout the study, although there were a number of minor short-term weight losses. Only one kitten (a male in the control group) showed a weight loss (9 grams) in the period from Day 0 to 7.

A small (5 mm or less) sore or scabbing was noted at the application site on Day 7 or later for one Group 4 (5X) male and one Group 4 (5X) female, and in one Group 3 (3X) female. In each case the lesion scabbed over and by Day 14 was barely detectable. It is stated (p. 17 of MRID 46513409) that the cause of these sores is unknown.

There was no indication of a dose-related effect involving food consumption, body weights or body weight gains. Although there were some sporadic statistically significant differences involving a few hematology and/or clinical chemistry parameters measured on Day 1, these were not biologically significant as these values were either within normal limits or were consistent with preexposure measurements, so there was no indication of any effect on these parameters.

This study utilized only 12-week old kittens weighing less than 5 lbs which were dosed with 1 mL of the test material. The proposed label directions specify a 2 mL dose on cats and kittens of 5 lbs and over. While there were no indications of any systemic toxicity in this study, the sores and scabbing noted in one 3X and two 5X kittens are consistent with scratching at the application site. Etofenprox is structurally similar to pyrethroids which are known to cause sensations (such as tingling, burning, itching or numbness) at dermal exposure sites. Fully-grown cats would tend to be capable of more vigorous scratching than 12-week old kittens, and they would be receiving a 2 mL dose.

TRB concludes that this companion animal safety study (OPPTS) is acceptable in demonstrating an adequate margin of safety (at least 5X) between the exposure associated with the proposed application rate for this formulation (1.0 mL) in <5 lb kittens between the age of 12 weeks and 6 months and that at which significant systemic effects may occur. However, it does not support the proposed use exposure level (2.0 mL) on adult cats weighing ≥ 5 lbs, as none of the animals tested were adults or in this weight category. The 870.7200 Guidelines specify that: "Studies should be performed on healthy dogs and cats representative of the classes of dogs and cats (size, weight range, sex, or age) for which the product is intended." In addition, there are concerns regarding the possibility of sores and scabbing following a 2.0 mL application. An appropriate study (including 1X, 3X and 5X multiples of 2.0 mL applications) should be submitted for adult cats >5 lbs as supporting data to fully support the proposed application rates of this product.

COMPLIANCE: Signed and dated Quality Assurance (p. 5), [No] Data Confidentiality (p. 2), and Good Laboratory Practice Compliance (p. 3) Statements were present.

I. MATERIALS

A. MATERIALS

1. Test material: RF2004 [CCSO], a liquid with active ingredients Etofenprox and Methoprene; assaying 40.23% Etofenprox and 3.53% (S)-Methoprene on May 13, 2004, and 40.30% Etofenprox and 3.55% (S)-Methoprene on September 17, 2004.
   Description: A liquid with a density of 0.9941 g/mL @ 20°C.
   Lot No.: ED271
   Storage: Room Temperature.

   Placebo: RF2004 [CCSO]. This formulation did not contain either Etofenprox or Methoprene.
   Description: A liquid
   Lot No.: ED270
   Storage: Room Temperature.

2. Administration: Topical (spot-on) on Day 0.

3. Test animals
   Species: Cat (Felis catus)
   Breed: Domestic shorthair
   Ages and weights at study initiation: Approximately 10 weeks of age at receipt and 12 weeks at dosing. On Day -1 males ranged from 1295 to 1765 g and females from 1068 to 1876 g.
   Source: Liberty Research, Waverly, New York
   Housing: Individually housed in stainless steel cages with solid floors, resting boards and litter pans.
   Diet: Lab Diet Feline Diet (No. 5003), *ad libitum*, except when the protocol required fasting (overnight, prior to scheduled blood collections).
   Water: "fresh tap water," *ad libitum*
   Environmental conditions:
   Temperature: 64-84°F (18-29°C).
   Humidity: 30-70%
   Air changes: At least 10 air changes per hour with 100% fresh air (no recirculation).
   Photoperiod: 12-hr light/dark cycle
   Acclimation period: "At least 2 weeks."

II. STUDY DESIGN

A. IN LIFE DATES

Start of Dosing: 3 August 2004; Last Data Collection: 17 August 2004

B. ANIMAL ASSIGNMENT/ DOSAGE AND ADMINISTRATION

There were a total of 12 kittens (6 males & 6 females) per dosage group. Each kitten in the Placebo Control Group (Group 1) was treated with 5 mL of the placebo formulation (which contained the same "inert" ingredients but was lacking the two actives -

Etofenprox and Methoprene - present in the test substance formulation). Kittens in Group 2 were treated with 1 mL of the test material; Group 3 with 3 mL of test material; and Group 4 with 5 mL test material.

Each kitten received the test material as a single dose. The site of application was on the mid back area between the shoulders (from p. 10 of MRID 46513409): "...the dorsal neck area of young adult cats.").

TABLE 1. Study design

		Number of Kittens	Amount Applied to Each Kitten	Mean Kitten Wt ± S.D. (g) on Day 0	Mean Dose mg/kg	Mean Dosage (mg/kg)	
						Etofenprox	S-Methoprene
Placebo Control	Male	6	5.0 mL[a]	1558 ± 92.9	3190[b]	0	0
	Female	6	5.0 mL[a]	1457 ± 250.4	3411[b]	0	0
1X	Male	6	1.0 mL[c]	1587 ± 138.1	626[d]	252	22.2
	Female	6	1.0 mL[c]	1441 ± 156.6	690[d]	278	24.5
3X	Male	6	3.0 mL[c]	1591 ± 161.5	1874[d]	754	66.5
	Female	6	3.0 mL[c]	1492 ± 229.6	1999[d]	804	71.0
5X	Male	6	5.0 mL[c]	1549 ± 163.2	3209[d]	1291	113.9
	Female	6	5.0 mL[c]	1420 ± 147.6	3500[d]	1408	124.3

Individual body weights given on p. 59 & 60 of MRID 46513409; means (with standard deviations) are presented on p. 22 and 23.

[a] Placebo

[b] Based on an assumed specific gravity for the placebo of 0.9941 g/mL (same as the proposed product)

[c] Test material (with actives); amount delivered.

[d] Based on a specific gravity for the test material of 0.9941 g/mL (see p. 91 of MRID 46513409)

C. DOSE SELECTION RATIONALE

From p. 12 of MRID 46513409: "The animals received 1, 3 or 5 mL of the test material or 5 mL of the control material as a single application." The test material dosage rates are the 1X, 3X and 5X dose levels for the label-specified dose rate of 1.0 mL for kittens weighing less than five pounds.

According to the proposed label the dosage rate would be 1 mL for cats weighing under 5 lbs and 2 mL for cats weighing 5 lbs and over. The formulation would be in disposable unidose applicators (presumably more than one per package), and application would be at one site.

D. EXPERIMENTAL DESIGN

From p. 13 of MRID 46513409: "Animals selected for use in this study were as uniform in age and weight as possible. They were young adult animals approximately 10 weeks of age at receipt and 12 weeks at initiation of dosing..." From p. 15: "Each animal was observed once each morning and afternoon throughout the study for viability. Clinical observations were conducted hourly on the first day of treatment for at least 4 hours after dosing... Animals received clinical observations twice daily the day after dosing

through the 14-day observation period... Body weights were measured four times prior to test material application, including once for randomization, once per week during the study, and at termination of the study... Food consumption was measured daily beginning approximately one week prior to study initiation."

E. PATHOLOGICAL PARAMETERS

Blood samples were collected from each kitten once predose (Day -5), and at 24 hours postdose from the cephalic vein following an overnight fast. The CHECKED (X) parameters were examined:

a. Hematology

X		X	
X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count		Absolute reticulocytes
	Blood clotting measurements		Percent reticulocytes
	(Thromboplastin time)		
	(Clotting time)		
X	(Prothrombin time [PT])*		
X	(Activated partial thromboplastin time [APTT])*		
	Erythrocyte morphology		

*Recommended in OPPTS 870.7200 Guidelines.

b. Clinical chemistry

X	ELECTROLYTES	X	OTHER
X	Calcium*	X	Albumin (Alb)*
X	Chloride*	X	Blood creatinine (Crea)*
	Magnesium	X	Blood urea nitrogen (BUN)*
X	Phosphorus*	X	Total Cholesterol
X	Potassium*	X	Globulin (Glob)*
X	Sodium*	X	Glucose (Gluc)*
		X	Total bilirubin (T Bil)*
	ENZYMES	X	Direct bilirubin (D Bil)*
X	Alkaline phosphatase(ALPor ALK)*	X	Total serum protein (TP)*
	Cholinesterase(ChE)	X	Triglycerides
X	Creatine phosphokinase		Serum protein electrophoresis
X	Lactate dehydrogenase(LDH)	X	Albumin/Globulin (A/G) ratio
X	Serum alanine aminotransferase (ALT or SGPT)*		Lipase
X	Serum aspartate aminotransferase(AST or SGOT)*		
X	Gamma glutamyl transferase(GGT)		
	Amylase		
	Glutamate dehydrogenase		

*Recommended in OPPTS 870.7200 Guidelines.

F. STATISTICS

From page 17 of MRID 46513409: "Group means and standard deviations were calculated for all numerical data, including body weights and clinical pathology parameters (excluding non-numerical data). The Levene Test was conducted on all

numerical data to determine whether there were equal variances among groups. If the Levene Test was not significant (equal variances) at $p > 0.05$, a Dunnett Test was conducted to identify statistically significant ($p < 0.05$) differences between treatment and control groups. If the Levene Test was significant (unequal variances) $p \leq 0.05$, the Steel Test (nonparametric procedure) was used to compare treatment groups to the control group."

G. DISPOSITION OF ANIMALS

None of the kittens died. From p. 18 of MRID 46513409: "No necropsies were conducted. The animals were transferred to facility stock after the 14-day observation period." According to the OPPTS 870.7200 Guidelines: "Routine sacrifice or necropsy is not required for surviving animals."

H. COMPLIANCE

Signed and dated Quality Assurance [p. 5], [No] Data Confidentiality [p. 2], and Good Laboratory Practice (GLP) Compliance [p. 3] Statements were present.

III. RESULTS

A. EXPOSURE LEVELS

Mean doses of the active ingredients by group and sex were the following: 1X: Males: 252 mg/kg Etofenprox; 22.2 mg/kg S-Methoprene; Females: 278 mg/kg Etofenprox; 24.5 mg/kg S-Methoprene; 3X: Males: 754 mg/kg Etofenprox; 66.5 mg/kg S-Methoprene; Females: 804 mg/kg Etofenprox; 71.0 mg/kg S-Methoprene; 5X; Males: 1291 mg/kg Etofenprox; 113.9 mg/kg S-Methoprene; Females: 1408 mg/kg Etofenprox; 124.3 mg/kg 124.3. Each kitten in the Placebo Control Group was treated with 5.0 mL placebo formulation (presumably containing the same "inert" ingredients as the test substance formulation but lacking the two actives - Etofenprox and S-Methoprene). Assuming the placebo formulation had 1) the same inerts as the test material and: 2) the same specific gravity as the test material, then kittens in this group were exposed to approximately 8.9X [1/0.5624 x 5] the dose of "inerts" that 1X kittens were exposed to (and approximately 1.78X the dose of "inerts" that 5X kittens were exposed to).

B. MORTALITY

There was no mortality. All kittens survived.

C. CLINICAL SIGNS

From p. 17 of MRID 46513409: "Clinical observations seen in all groups included sporadic diarrhea and soft feces. These are common observations in cats. A clinical observation of excessive salivation was noted for one male and one female from Group 1 [placebo control] a few minutes after dosing and for one male at approximately 20 minutes after dosing [according to information on p. 51 control material was noted on this kitten's right shoulder and forearm]. One Group 1 [control] female was observed with salivation at the 1-hour observation and one Group 4 [5X] female at the 2-hour observation. The salivation lasted no more than approximately 10 minutes for the animals. The salivating was not noted at any other time points. The two groups that

were noted with salivation received the largest amount of the control or test material, 5-mL. The salivation was probably due to oral contact with the control or test material."

"A small sore/scabbing 95 mm or smaller) area on the mid-dorsal back (between shoulders) at the site of application was noted on Day 7 or later for one Group 4 [5X] male, one Group 3 [3X] female and one Group 4 [5X] female. The area scabbed over and, by Day 14 of the study, it was barely detectable. The cause of the sores in unknown." From information on p. 54 the Group 4 male [400132] had a sore (or sores) on the dorsal back at the site of application (mid back area between shoulders) which was first noted at the AM observation on Day 7; the sore was initially approximately 5 mm in size and it became a scabbed area that was barely detectable by Day 14 of the study. From information on p. 57 the 3X female [400147] had a sore/scab on the middle of the back which was first noted at the AM observation on Day 8; again, the sore was initially approximately 5 mm in size and became a scabbed area that was barely detectable by Day 14 of the study. From information on p. 58 the 5X female [400157] had a sore at the application site which was first noted at the AM observation on Day 7; the sore was initially about 5 mm in size and became a scabbed area that was barely detectable by Day 14 of the study.

Occurrences of soft feces and diarrhea were sporadic. They were observed in one control male [#400111] on Day 6, in two 5X [#400129 and #400130] males on Day 2, and then again in these two males after Day 9, in a 1X female [#400145] in the period from Day 10 through Day 12, and in a 3X female [#400146] on Days 9 and 10.

TABLE 2. Clinical Observations in Kittens Treated with RF2004 [CCSO] Following Treatment[a]

Time and Observation	Group 1 Placebo (Vehicle) Control (5 mL)	Group 2 1X (1 mL)	Group 3 3X (3 mL)	Group 4 5X (5 mL)
Day 0 (1-4 hrs after treatment): Excessive salivation:	0/6M, 1/6F	0/6M, 0/6F	0/6M, 0/6F	0/6M, 1/6F
Days 2-14: Diarrhea or soft feces:	1/6M, 2/6F	0/6M, 1/6F	0/6M, 1/6F	2/6M, 0/6F
Days 7-14: Sore or scab at application site:	0/6M, 0/6F	0/6M, 0/6F	0/6M, 1/6F	1/6M, 1/6F

[a]Data taken from Table A, Individual Clinical Signs, pp. 51-58 of MRID 46513409.

Kittens which showed sore and/or scab at the application site in the period from Day 7 to Day 14 were the following (from p. 54, 57 & 58 of MRID 46513409): Males: Placebo: (none); 1X: (none); 3X: (none); 5X: (400132); Females: Placebo: (none); 1X: (none); 3X (400147); 5X: (400157).

D. BODY WEIGHT AND WEIGHT GAIN

From p. 17 of MRID 46513409: "There was (sic) no statistically significant differences in body weights for all groups when compared to the controls. All animals gained weight throughout the study."

TABLE 3. Mean Body Weights for Kittens by Group				
Group	g ± S.D.			
	Day -1	Day 0	Day 7	Day 14
Control Males	1536 ± 110.3	1558 ± 92.9	1727 ± 167.2	1952 ± 154.0
Control Females	1431 ± 266.7	1457 ± 250.4	1591 ± 258.8	1743 ± 309.7
1X Males	1544 ± 145.8	1587 ± 138.1	1750 ± 139.5	2109[a] ± 473.8
1X Females	1426 ± 164.1	1441 ± 156.6	1560 ± 146.9	1732 ± 157.8
3X Males	1557 ± 161.6	1591 ± 161.5	1717 ± 193.6	1920 ± 215.6
3X Females	1437 ± 224.5	1492 ± 229.6	1609 ± 230.8	1781 ± 199.9
5X Males	1523 ± 129.8	1549 ± 163.2	1668 ± 163.0	1881 ± 217.5
5X Females	1403 ± 129.3	1420 ± 147.6	1493 ± 169.5	1649 ± 159.0

Values from Tables 3 & 4 (p. 22-23) of MRID 46513409.

[a]As reported on p. 22; however, individual body weight data (p. 59) indicate that kitten 400121 had a rather incredible 1187 g weight increase (from 1848 to 3035 g) in the period from Day 7 to 14. If this kitten actually gained only 187 g (more consistent with the weight gains of other male kittens) then the mean body weight ± S.D. for 1X males on Day 14 would be 1943 ± 144.4.

There were no significant differences between groups with respect to mean body weight gains:

TABLE 4. Mean Body Weight Gains for Kittens by Group[a]				
Group	g ± S.D.			
	Day -1 to 0	Day 0 to 7	Day 7 to 14	Day 0 to 14
Control Males	23 ± 61.0	169 ± 96.2	225 ± 180.1	394 ± 166.5
Control Females	26 ± 30.5	134 ± 24.7	152 ± 77.7	286 ± 90.0
1X Males	44 ± 22.4	162 ± 22.1	360[b] ± 405.8	522[b] ± 423.6
1X Females	15 ± 20.6	120 ± 59.4	171 ± 11.6	291 ± 63.8
3X Males	35 ± 45.7	125 ± 40.9	203 ± 32.6	328 ± 62.2
3X Females	55 ± 31.5	118 ± 21.8	171.8 ± 50.7	289 ± 59.0
5X Males	26 ± 60.0	119 ± 57.3	213 ± 71.5	332 ± 104.1
5X Females	17 ± 42.1	73 ± 44.5	156 ± 33.1	229 ± 54.0

[a]Calculated by this reviewer from values from Tables A-9 and A-10 p. 59-60 of MRID 46513409.

[b]Calculated using the day 14 weight (3035 g) reported on p. 59 for Group 2 (1X) male 400121; if the weight was actually 2035 g (consistent with values for other 5 male 1X kittens) then the weight gain for this group from Day 7 to 14 was 193 ± 21.6 g, and from Day 0 to 14 was 356 ± 23.7 g.

E. FOOD CONSUMPTION

From p. 18 of MRID 46513409: "A statistically significant difference from the control group was noted for Group 3 [3X] males on Day -7, pretest. The Group 3 consumption was slightly higher then (sic) the other groups. There were no other statistically significant differences noted."

TABLE 5. Mean Food Consumption (g/kitten/day) by Group

Group	g ± S.D.						
	Day -1	Day 0	Day 2	Day 3	Day 4	Day 5	Day 7
Control Males	76.7 ± 21.5	79.8 ± 11.1	99.3 ± 60.4	87.2 ± 11.9	84.2 ± 24.1	89.2 ± 16.7	93.5 ± 6.6
Control Females	75.8 ± 34.6	65.6 ± 8.7	81.0 ± 31.2	72.0 ± 18.5	88.7 ± 32.5	76.2 ± 17.1	89.8 ± 37.8
1X Males	96.7 ± 52.3	79.0 ± 14.5	99.2 ± 22.3	80.3 ± 10.8	89.2 ± 20.8	84.7 ± 18.1	109.7 ± 48.3
1X Females	90.7 ± 32.9	72.7 ± 7.4	93.3 ± 11.4	77.7 ± 12.1	91.0 ± 11.9	97.8 ± 68.5	90.5 ± 11.8
3X Males	55.5 ± 11.0	90.0 ± 10.8	90.0 ± 16.7	84.8 ± 15.7	97.5 ± 20.0	93.3 ± 27.2	97.5 ± 14.3
3X Females	77.5 ± 45.3	76.8 ± 21.3	101.5 ± 32.1	79.0 ± 23.5	95.0 ± 26.9	120.2 ± 81.8	98.2 ± 19.6
5X Males	67.3 ± 29.1	69.7 ± 14.0	89.8 ± 21.7	85.5 ± 19.9	92.2 ± 19.6	76.2 ± 22.6	108.2 ± 18.5
5X Females	97.0 ± 36.4	68.8 ± 9.0	80.0 ± 18.4	46.2 ± 17.4	70.3 ± 19.6	95.2 ± 44.4	90.5 ± 27.0

[a]Calculated by this reviewer from values from Tables A-11 and A-12 p. 61-62 and 64-65 of MRID 46513409.

As indicated in the Table above, Group 4 (5X) females had a somewhat lower mean food consumption on Day 3 relative to their controls and the females in Groups 2 (1X) and 3 (3X). However, it is unlikely that this was due to treatment as there was no significant difference between mean food consumption values for Group 4 females and their controls on Day 2 (80.0 vs. 81.0 g).

F. HEMATOLOGY

The performing laboratory (Ricerca Biosciences, LLC, Concord, OH 44077-1000) did not provide any reference ranges for cat (or kitten) hematology parameters

The report states (p. 18) that: "A statistically significant difference from the controls for mean corpuscular volume was noted for Group 3 males on Day 1, but this value was within normal range."

TABLE 6. Mean Corpuscular Volume (MCV) in Kittens by Group[a]		
Group	fL ± S.D.	
	Day -5	Day 1
Control Males	46.9 ± 1.8	45.1 ± 1.5
Control Females	45.0 ± 1.8	42.7 ± 2.3
1X Males	46.4 ± 1.9	44.7 ± 1.7
1X Females	46.0 ± 2.0	44.3 ± 1.9
3X Males	45.3 ± 2.6	42.2[b] ± 1.8
3X Females	45.1 ± 1.3	43.4 ± 1.7
5X Males	46.0 ± 1.8	44.6 ± 2.0
5X Females	45.8 ± 2.5	44.2 ± 1.7

[a]Calculated by this reviewer from values from Tables A-13, A-14, A-15 and A-16 p. 67-70 of MRID 46513409.
[b]Reported as being "significantly different" from control value.

According to http://www.ahc.umn.edu/rar/RefValues.html the normal reference range for MCV in the cat is 65-80 fL, but another reference [http://www.vet.purdue.edu/vm525/fall 2002/reference_ranges.pdf] gives a range of 40-55 fL, and this was observed in this study (the range of values seen in this study for Day -5 was 42.1-49.6; while the range for Day 1 was 39.6 to 47.3; on Day 1 the low value was observed in a Group 3 male; none of the other kittens had a value for MCV of below 40.0). It is concluded that exposure to the test material had no biologically relevant effect on this parameter.

In addition, there was no indication of an effect involving RBC counts or HGB:

TABLE 7. Mean RBC and HGB values for Kittens by Group[a]				
Group	RBC ± S.D. (M/µL)		HGB ± S.D. (g/dL)	
	Day -5	Day 1	Day -5	Day 1
Control Males	7.06 ± 0.71	7.03 ± 0.79	9.8 ± 1.2	10.0 ± 1.1
Control Females	7.59 ± 1.08	7.58 ± 0.59	10.3 ± 1.4	10.3 ± 0.6
1X Males	6.93 ± 0.59	7.03 ± 0.79	9.6 ± 0.6	10.0 ± 1.1
1X Females	7.06 ± 0.76	7.62 ± 0.59	9.5 ± 0.8	10.3 ± 0.6
3X Males	6.94 ± 0.89	6.77 ± 0.45	9.2 ± 0.7	9.1 ± 0.3
3X Females	7.08 ± 1.15	7.20 ± 1.0	9.7 ± 1.5	9.8 ± 1.2
5X Males	6.89 ± 0.38	6.80 ± 0.76	9.6 ± 0.4	9.6 ± 0.7
5X Females	7.11 ± 0.88	7.02 ± 0.86	9.7 ± 0.9	9.8 ± 0.9

[a]Calculated by this reviewer from values in Tables A-13, A-14, A-15 and A-16 p. 67-70 of MRID 46513409.

According to http://www.vet.purdue.edu/vm525/fall 2002/reference_ranges.pdf the normal reference range for RBC's in the cat is 5.0 to 10.0 x 10^6/µL; all individual measurements fell within this reference range. For HGB the same reference gives 8 to 15 g/dL as the normal range in the cat; one Group 3 female [400148] had a pretest value (7.7) below the minimum value of this reference range; while one Group 2 male [400121] had a postdose value of 6.9. As this was an isolated occurrence, and there was no indication of a dose relationship, it is concluded that there was no evidence of an effect involving treatment with the test material.

From http://www.vet.purdue.edu/vm525/fall 2002/reference_ranges.pdf the normal reference ranges for Prothrombin Time (PT) and Partial Thromboplastin Time (PTT or APTT) in the cat are 6.4 to 9.6 seconds and 9.3 to 18.7 seconds, respectively. A considerable number of the individual measurements (as well as the means) were somewhat elevated, possibly related to the fact that these were kittens rather than adult cats. However, Group means for Day -5 were generally similar to those of Day 1, and so there was no indication that treatment with the test material had any effect (adverse or otherwise) involving these parameters. It is reported (p. 30 and 32) that APTT was significant (presumably there was a significant dose trend) in males on both Days -5 and 1.

TABLE 8. Mean PT and APTT values for Kittens by Group[a]

Group	PT ± S.D. (Seconds)		APTT ± S.D. (Seconds)	
	Day -5	Day 1	Day -5	Day 1
Control Males	9.6 ± 0.4	9.9 ± 0.5	16.1 ± 4.1	18.0 ± 3.1
Control Females	10.1 ± 0.4	10.1 ± 0.6	17.6 ± 7.5	24.6 ± 13.5
1X Males	9.9 ± 0.4	10.1 ± 0.5	16.2 ± 3.8	17.1 ± 6.1
1X Females	10.1 ± 0.6	10.2 ± 0.4	24.5 ± 15.8	22.9 ± 14.3
3X Males	9.9 ± 0.4	10.2 ± 0.5	23.8 ± 11.6	26.0 ± 13.2
3X Females	10.4 ± 0.6	10.1 ± 0.5	21.7 ± 8.3	20.6 ± 9.0
5X Males	9.8 ± 0.6	9.8 ± 0.8	22.1 ± 7.9	20.9 ± 7.2
5X Females	10.1 ± 0.4	10.2 ± 0.5	24.1 ± 13.5	16.3 ± 3.8

[a]Individual values in Tables A-13, A-14, A-15 and A-16 p. 67-70; means and standard deviations in Tables 7, 8, 9 & 10, p. 30-34 of MRID 46513409.

For leukocyte counts there were no significant differences in either sex between the placebo and test-material exposed groups at 24 hours postdose. According to http://www.ahc.umn.edu/rar/RefValues.html the normal reference range for leukocytes in the cat is 3.8-19 K/mm^3; [http://www.vet.purdue.edu/vm525/fall 2002/reference_ranges.pdf, gives a similar range of 6.0-18.0 K/mm^3]. The ranges observed in this study were: males:10.68-24.22 (Day -5); 10.31-20.84 (Day 1); females: 12.74-21.67 (Day -5) and 7.78-22.43 (Day 1). As these were kittens (rather than adults) ranges might be somewhat different from the "normal" reference ranges.

There was also no indication of an effect involving any of the remaining hematology parameters.

G. CLINICAL CHEMISTRY

The performing laboratory (Ricerca Biosciences, LLC, Concord, OH 44077-1000) did not provide any reference ranges for cat (or kitten) clinical chemistry parameters

The report states (p. 18) that: "On Day 1 there were statistically significant differences from the control noted for Group 4 male sodium and chloride, Group 2 and 3 female potassium and Group 3 female creatinine. All of these differences were minor and within normal ranges."

TABLE 9. Mean Na and Cl values for Kittens by Group[a]

Group	Na ± S.D. (MEq/L)		Cl ± S.D. (MEq/L)	
	Day -5	Day 1	Day -5	Day 1
Control Males	153.0 ± 2.8	150.8 ± 1.2	118.3 ± 2.7	118.0 ± 1.8
Control Females	155.7 ± 1.5	154.2 ± 1.5	120.8 ± 1.2	121.3 ± 1.2
1X Males	153.2 ± 1.5	152.7 ± 1.6	118.5 ± 1.4	119.5 ± 1.9
1X Females	154.5 ± 3.2	155.0 ± 2.4	120.3 ± 2.4	122.7 ± 1.9
3X Males	153.7 ± 1.4	152.2 ± 0.8	119.2 ± 2.1	119.7 ± 0.8
3X Females	155.2 ± 2.3	152.0 ± 0.9	120.8 ± 2.7	119.3 ± 1.2
5X Males	153.0 ± 2.9	153.0 ± 1.4	118.7 ± 3.0	120.5[b] ± 2.0
5X Females	155.2 ± 4.7	153.2 ± 1.9	121.5 ± 3.8	121.5 ± 1.4

[a]Individual values in Tables A-25, A-26, A-27 and A-28 p.78, 81, 84 and 87; group mean values in Tables 15, 16, 17 and 18, p. 38, 41, 44 and 47 of MRID 46513409.
[b]Reported (p. 44) as being statistically significantly different from control group at $p \leq 0.05$.

According to http://www.vet.purdue.edu/vm525/fall 2002/reference_ranges.pdf the normal reference range for sodium in the cat is 148-157 mmol/L, and for chloride is 115-128 mmol/L. The range of pretest sodium values in this study was 149-162 mEq/L and for postexposure 149-159 mEq/L; only a single Group 2 (1X) female (#400143) had a postexposure value (159 mEq/L) outside this reference range. The range of individual preexposure chloride values in this study was 115-126 mEq/L and for postexposure was 115-126 mEq/L. This reviewer concludes that there is no indication of an effect on either of these two clinical chemistry parameters.

There was also no indication of an effect involving any of the remaining clinical chemistry parameters.

TABLE 10. Mean K and Creatinine values for Kittens by Group[a]				
Group	K ± S.D. (MEq/L)		Creatinine ± S.D. (mg/d/L)	
	Day -5	Day 1	Day -5	Day 1
Control Males	6.3 ± 0.31	5.9 ± 0.43	0.5 ± 0.10	0.5 ± 0.14
Control Females	5.9 ± 0.45	6.2 ± 0.17	0.5 ± 0.10	0.6 ± 0.10
1X Males	5.9 ± 0.28	5.6 ± 0.31	0.5 ± 0.10	0.5 ± 0.08
1X Females	5.6 ± 0.30	5.6* ± 0.29	0.5 ± 0.08	0.6 ± 0.08
3X Males	5.9 ± 0.29	6.0 ± 0.33	0.5 ± 0.14	0.6 ± 0.10
3X Females	6.1 ± 0.87	5.6* ± 0.55	0.5 ± 0.08	0.4** ± 0.09
5X Males	5.8 ± 0.36	6.1 ± 0.39	0.4 ± 0.17	0.6 ± 0.15
5X Females	6.3 ± 0.53	6.0 ± 0.47	0.5 ± 0.08	0.6 ± 0.06

[a]Individual values in Tables A-25, A-26, A-27 and A-28 p.78, 81, 84 and 87; group mean values in Tables 15, 16, 17 and 18, p. 38, 41, 44 and 47 of MRID 46513409.
*Reported (p. 47 of MRID 46513409) as statistically significantly different from controls with $p \leq 0.05$.
**Reported (p. 47 of MRID 46513409) as statistically significantly different from controls with $p \leq 0.01$.

According to http://www.vet.purdue.edu/vm525/fall 2002/reference_ranges.pdf the normal reference range for potassium (K) in the cat is 3.5-5.1 mmol/L; however, these were kittens rather than adult cats, and this may have been a factor in these slightly elevated values. Exposure to the test material was not a factor as the values for potassium were somewhat elevated on Day -5, and the Day 1 mean values at 1X and 3X (statistically significantly different from the control value) were actually closer to the normal reference range. For creatinine, the normal reference range in cats is given (same citation as for K) as 0.9-2.3 mg/dL; an elevated value can be a result of renal failure, urinary obstruction, dehydration or hyperthyroidism, but a depressed value (as seen in this study) is not associated with any pathology.

H. NECROPSY FINDINGS

There were no necropsies. Because none of the kittens died or were sacrificed in a moribund state, no necropsies were necessary. According to the OPPTS 870.7200 Companion Animal Safety Guidelines: "Routine sacrifice or necropsy is not required for surviving animals."

IV. DISCUSSION

In a companion animal safety study (MRID 46513409), 4 groups, each containing 12 (6/sex) approximately 12-week old "young adult animals" (source: Liberty Research, Waverly, NY; males: 1295-1765 g; females: 1068-1876 g) were treated at 0X (Group 1: 5.0 mL of the formulation without active ingredients); 1X (Group 2: 1.0 mL); 3X (Group 3: 3.0 mL); and 5X (Group 4: 5.0 mL) of the proposed product with actives. The test material was applied to an area on the mid-dorsal back (between shoulders) on Day 0, with subsequent 14-day observation.

According to proposed label directions the product would be applied to the fur of the cat or kitten on the back of the neck at the base of the skull. Labeling specifies the use of a 1 mL dose for cats and kittens weighing less than 5 lbs, and a 2 mL dose for cats or kittens weighing more than 5 lbs.

On the day of dosing (Day 0); four clinical observations were made at 1, 2, 3 and 4 hours after postdose. Otherwise, clinical observations were conducted twice daily, once in the AM and once in the PM [approximately x hours apart].

Individual body weights were measured on Days -12, -5, -1, 0, 7 and 14. Individual food consumption was measured on a daily basis for Days -7, -6, -4 and then daily thereafter through Day 14. Blood samples were taken once pretest (Day -5) and then on Day 1 (approximately 24 hours postdose).

There was no mortality and there was no indication of systemic toxicity. Clinical observations seen in all groups included sporadic diarrhea and soft feces. Observations of excessive salivation were noted in one male and one female of the control group a few minutes after dosing, and for one male in this group about 20 minutes after dosing. One control female had salivation at the 1-hour observation and one 5X female showed this at the 2-hour observation. These episodes of salivation lasted no more than 10 minutes, and are ascribed (see p. 17 of MRID 46513409) to oral contact (ingestion) with the control or test material.

Overall, all cats gained weight throughout the study, although there were a number of minor short-term weight losses. Only one cat (a male in the control group) showed a weight loss (9 grams) in the period from Day 0 to 7.

A small (5 mm or less) sore or scabbing was noted at the application site on Day 7 or later for one Group 4 (5X) male and one Group 4 (5X) female, and in one Group 3 (3X) female. In each case the lesion scabbed over and by Day 14 was barely detectable. It is stated (p. 17 of MRID 46513409) that the cause of these sores is unknown.

There was no indication of any dose-related effect involving food consumption, body weights or body weight gains. Although there were some sporadic statistically significant differences involving a few hematology and/or clinical chemistry parameters as measured on Day 1, these were not biologically significant as these values were either within normal limits or were consistent with preexposure measurements, so there was no indication of any effect on these parameters.

This study utilized only 12-week old kittens weighing less than 5 lbs which were dosed with 1 mL of the test material. The proposed label directions specify a 2 mL dose on cats and kittens of 5 lbs and over. While there were no indications of any systemic toxicity in this study, the sores and scabbing noted in one 3X and two 5X kittens are consistent with scratching at the application site. Etofenprox is structurally similar to pyrethroids which are known to cause sensations (such as tingling, burning, itching or numbness) at dermal exposure sites. Fully-grown cats >5 lb. would be capable of more vigorous scratching than 12-week old kittens, and they would be receiving a 2 mL dose.

TRB concludes that this companion animal safety study (OPPTS) is acceptable in demonstrating an adequate margin of safety (at least 5X) between the exposure

associated with the proposed application rate for this formulation (1.0 mL) in <5 lb kittens between the age of 12 weeks and 6 months and that at which significant systemic effects may occur. However, it does not support the proposed use exposure level (2.0 mL) on adult cats weighing ≥ 5 lbs, as none of the animals tested were adults or in this weight category. The 870.7200 Guidelines specify that: "Studies should be performed on healthy dogs and cats representative of the classes of dogs and cats (size, weight range, sex, or age) for which the product is intended." In addition, there are concerns regarding the possibility of sores and scabbing following a 2.0 mL application. An appropriate study (including 1X, 3X and 5X multiples of 2.0 mL applications) should be submitted for adult cats >5 lbs as supporting data to fully support the proposed application rates of this product.

ACUTE TOX ONE-LINERS

1. **DP BARCODE:** D316839
2. **PC CODES:** 128965 (Etofenprox), 105402 (S-Methoprene)
3. **CURRENT DATE:** August 24, 2005
4. **TEST MATERIAL:** 40.3 Etofenprox and 3.55% (S)-Methoprene, consistent with the label declaration (40.0% Etofenprox, 3.6% S-Methoprene) for the proposed product RF2004 [CCSO]

Study/Species/Lab Study #/Date	MRID	Results	Tox. Cat.	Core Grade
Companion animal/12-wk old kittens/ Ricerca Biosciences, LLC, Concord OH 44077-1000/ Study No. 016064; Wellmark International No. 2971/Study Completed Dec. 8, 2004	46513409	4 groups (each containing 6M & 6F) of approximately 12-wk old kittens (M: 1295-1765 g; F: 1068-1876 g) were treated at 0X (5.0 mL formulation without actives); 1X (1.0 mL test material); 3X (3.0 mL test material) and 5X (5.0 mL) applied to an area on the mid-dorsal back (between the shoulders), consistent with proposed label instructions to apply to the back of the neck at the base of the skull. Kittens were observed for 14 days following treatment, with blood taken for hematology & clinical chemistry on Days -5 and +1. There was no mortality and there was no indication of systemic toxicity. Clinical observations in all groups included sporadic diarrhea and soft feces. Excessive salivation was seen in one male and one female of control group a few minutes after dosing and in another male of this group about 20 minutes after dosing. One 5X female showed similar salivation at the 2-hr observation; all episodes were short term (less than 10 minutes) and were ascribed to oral contact with the test material. Small (5 mm or less) sores/scabs were noted at the application site on Day 7 or later for one 5X male and one 5X female, and for one 3X female, consistent with scratching at application site. There was no indication of any biologically significant effect involving food consumption, body weights, body weight gains, hematology and/or clinical chemistry parameters. Study supports proposed use of formulation (1.0 mL) in kittens (from 12 weeks to 6 months of age) weighing less than 5 lbs; however, it does not support the proposed use exposure level (2.0 mL) for adult cats, particularly those weighing >5 lbs, as these were not included in the study.	N/A	N/A

Core Grade Key: **A =Acceptable, S = Supplementary, U = Unacceptable, V = Self Validated**